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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/993,314 | 11/05/2001 | Theo T. Nikiforov | 01-054410US | 5637 |

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| EXAMINER | |
|---|---|
| LAM, ANN Y | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1641 | |

DATE MAILED: 12/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/993,314 | NIKIFOROV ET AL. | |
| | Examiner | Art Unit | |
| | Ann Y. Lam | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *34-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-33* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election without traverse of group I (claims 1-33) in the reply filed on September 27, 2004 is acknowledged.

### *Claim Objections*

Claims 26 and 27 are objected to because of the following informalities: claims 26 and 27, both should include –further—before "comprising". Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8-11, 14, 19-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp, WO 98/45481, in view of Yon-Hin et al., 6,440,645.

Knapp teaches the invention substantially as claimed. More specifically, as to claim 1, Knapp discloses a method of performing a mobility shift assay in a microfluidic device, the method comprising:

flowing a reaction mixture comprising an enzyme (page 43, line 30), an enzyme substrate (page 43, line 30), and a product (i.e., assay of enzyme and substrate, page 43, lines 29-30, also page 44, line 5) through a separation region of the microfluidic device (i.e., purification or separation, page 17, line 24, and page 18, second full paragraph) under an applied pressure (micropumps, page 71, third full paragraph); and,

detecting at least one of the separated materials, thereby performing the mobiity shift assay in the microfluidic device (page 75, second full paragraph.) Examiner notes that the mobility shift assay as disclosed and claimed by Applicant is essentially a method of mixing reagents, and a separation or purification step followed by detection of one of the reagents or the product to determine if it is present.

As to claim 2, the at least one other material comprises the enzyme and/or unreacted enzyme substrate (page 43, line 30).

As to claim 3, the materials are flowed in an absence of an applied electric field (page 71, third full paragraph, disclosing micropumps as an alternative to an electroosmotic system (page 72, first paragraph.)

As to claim 4, at least the separated materials are flowed in the microfluidic device under at least one simultaneously applied electric field (page 65, second full paragraph.)

As to claim 5, one or more of the separated materials comprise a label (page 75, second full paragraph).

As to claim 6, a microchannel comprises the separation region (1340, page 79, line 9, see figure 13).

As to claim 8, the detecting step comprises fluorescent detection (page 28).

As to claim 14, the method further comprises sampling the reaction mixture from a source external to the microfluidic device (using electropipette, 1395, page 78, last paragraph).

As to claim 19, prior to the flowing step, the method comprises:

flowing at least the enzyme through a first channel (e.g., 1355, in figure 13) in fluid communication with an enzyme source (e.g., 1390) into a mixing region (13103, page 78, last paragrah) of the microfluidic device; and,

flowing at least the enzyme substrate through a second channel (e.g., 1350, in figure 13) in fluid communication with an enzyme substrate source (e.g., 1385) into the mixing region (13103), wherein the enzyme converts at least some of the enzyme substrate to the product, thereby producing the reaction mixture.

As to claim 20, a microchannel (13103) comprises the mixing region (figure 13). (The mixing chamber 13103 is also considered a microchannel.)

As to claim 29, the flow step further comprises flowing eluents (e.g., the solvent in a reagent in liquid form, page 81, line 16) or separation buffer (page 81, line 23) into the separation region from one or more microchannels in fluid communication with the separation region.

As to claim 30, the method includes varying a concentration of the one or more eluents or separation buffers flowed into the separation region to control separation of materials within the separation region (page 71, third full paragraph, disclosing a micropump for controlling the flow of materials in the device.)

As to claims 31 and 32, the method further comprises sampling the enzyme, the enzyme substrate, and/or an additional material from one or more sources external to the microfluidic device (see page 56, disclosing electropipettors for introducting reagents into a microfluidic apparatus.) (Examiner notes that claim 32 recites limitations relating to an element, i.e., the "additional material", in claim 31 that is only recited in the alternative.)

As to claim 33, the one or more sources are present in a microtiter dish (page 56, first line), and the microfluidic device comprises one or more external capillary elements (e.g., 1355, in figure 13) in fluid communication with the separation region (13103, page 78, last paragrah), wherein the method comprises contacting the one or more external capillary elements to the one or more source and drawing fluid out of the one or more sources, into the one or more external capillary elements, and into the microfluidic device (see page 56, disclosing electropipettors for introducing reagents into a microfluidic apparatus.)

Knapp discloses that the virtually any set of reagent, including enzymes and substrates, can be sampled and assayed in the microfluidic device disclosed (page 43, lines 28-34.) Knapp also discloses purification or separation steps in general on page 17, line 24, and page 18, second full paragraph, and specifically discloses a channel

(2043, fig. 20) for gel electrophoresis as an embodiment for separation for use in DNA sequencing (page 82, lines 32-33, and see also page 83, second full paragrah.)

However, Knapp does not disclose an embodiment wherein the separation means comprises ion-exchange material for separating the product from at least one other material based upon a net charge difference between the product and the at least one other material to produce separated materials.

Similar to Knapp, Yon-Hin discloses a microfluidic device having sample reservoirs (1), a reaction or mixing chamber (2), (see figure 2), and a separation channel (8), (see fig. 4-6, and col. 5, lines 20-37.) Yon-Hin teaches that separation procedures such as electrophoresis or chromatography may be performed on the microchannels (col. 4, lines 3-64.)

As to claim 9, Yon-Hin discloses a plurality of microbeads or a gel comprising ion-exchange material (see charged species, figures 5-6, and col. 5, lines 20-21, 26-37.)

As to claim 10, an inner surface of the separation region comprises the ion-exchange material (col. 5, line 23).

As to claims 11 and 21-28, the ion-exchange material is coated on an inner surface of the separation region (col. 5, line 23). (Claims 21-28 appear to be reciting limitations regarding a process of making the separation region. Since Applicant is claiming a method of using a device, i.e., with the device fully formed with the ion-exchange material in the separation region, claims 21-28 therefore are anticipated by the reference since the reference discloses the fully formed device. Also, as to claim

26, Examiner interprets a plurality of chromatographic materials to include "other chromatographic materials".)

Yon-Hin discloses that the charged materials is used for ion exchange chromatographic separation (col. 5, lines 20-21 and 36-37.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide for ion-exchange chromatographic separation as taught by Yon-Hin as the specific separation mechanism that is disclosed in general in the Knapp device, as a well known and conventional means of separating materials with opposite charges, as taught by Yon-Hin.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp, WO 98/45481, in view of Yon-Hin et al., 6,440,645, as applied to claim 1, and further in view of Pourahmadi, 6,440,725.

Knapp in view of Yon-Hin disclose the invention substantially as claimed (see above with respect to claim 1), except for the applied pressure being produced by a vacuum pump operably connected to the microfluidic device through a port that fluidly communicates with the separation region.

Both Knapp and Yon-Hin disclose use of pumps to move fluids in the microfluidic device (see Knapp, page 71, third full paragraph; and Yon-Hin, col. 5, line 42.) However, neither Knapp nor Yon-Hin disclose a vacuum pump as the specific type of pump.

Pourahmadi discloses a microfabricated chip having channels (col. 2, lines 53-54), for assay of biochemicals (col. 5, lines 11-14). Pourahmadi further teaches use of vacuum pumps to move fluids within the device (col. 8, lines 46-52), as an alternative to other means such as electrophoretic or electroosmotic means to move fluid (col. 8, lines 55-56). It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a vacuum pump as the specific type of pump used in the method disclosed by Knapp in view of Yon-Hin, as a conventional pumping means for moving fluid in a microchannel as taught by Pourahmadi.

Claim is 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp, WO 98/45481, in view of Yon-Hin et al., 6,440,645, as applied to claim 1, and further in view of Matsudaira et al., 4,448,493.

Knapp in view of Yon-Hin disclose the invention substantially as claimed (see claim 1 above). More specifically, Yon-Hin teaches that polyacrylamide is a known chromatographic media for ion exchange chromatography (col. 5, line 29.) However, neither Knap nor Yon-Hin specifically disclose that the polyacrylamide is modified.

Matsudaira, like Yon-Hin, teaches ion-exchange resins (col. 6, line 60 – col. 7, line 10), with resin binders such as polyacrylamide (col. 7, lines 29-31.) The Matsudaira polyacrylamides are considered to be modified by the ion-exchange resins, allowing for ion-exchange.

It would have been obvious to one of ordinary skill in the art to provide the ion-exchange resins on the polyacrylamide taught by Knapp in view of Yon-Hin, as a well-known and conventional means for providing ion-exchange capability to polyacrylamide, as taught by Matsudaira.

Alternatively, since Matsudaira further teaches modifying the resin binders (and thus the polyacrylamide) to obtain high-polymeric binders that are soluble in water (col. 7, lines 27-33), it would have been obvious to one of ordinary skill in the art to modify the polyacrylamide in the device taught by Knapp in view of Yon-Hin, as taught by Matsudaira to provide for water soluble ion-exchange material, as would be desirable for use with water soluble samples and reagents.

Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp, WO 98/45481, in view of Yon-Hin et al., 6,440,645, as applied to claim 1, and further in view of Norman et al., 6,329,357.

Knapp in view of Yon-Hin disclose the invention substantially as claimed (see above with respect to claim 1.) More specifically, Knapp in view of Yon-Hin teach use of a microchannel filled with ion exchange material for separation of materials in an assay including an enzyme and substrate in general (see claim 1 above), but do not specifically disclose that the enzyme is a protein kinase.

Norman discloses an assay useful for discovering compounds for treating vitamin D disorders (col. 34, lines 46-48). The assay includes a protein kinase (col. 39, line 19)

and use of ion-exchange material to separate the phosphorylated product from the remaining materials (col. 40, lines 34-36.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the device and method taught by Knapp in view of Yon-Hin to perform the assay taught by Norma, as would be desirable for discovering compositions useful for treating vitamin D disorders as taught by Norman.

Claims 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knapp, WO 98/45481, in view of Yon-Hin et al., 6,440,645, as applied to claim 1, and further in view of Beers et al., 5,508,273.

Knapp in view of Yon-Hin disclose the invention substantially as claimed (see above with respect to claim 1.) More specifically, Knapp in view of Yon-Hin teach use of a microchannel filled with ion exchange material for separation of materials in an assay including an enzyme and substrate in general (see claim 1 above), but do not specifically disclose that the enzyme is a protein phosphatase.

Beers discloses an assay method for the inhibition of the activity of tyrosyl protein phosphatase (col. 6. lines 66-67) useful for discovering compounds to treat bone wasting diseases (col. 6, lines 37-38.) The assay method includes incubating tyrosyl acid phosphatase with a substrate and subsequently passing the mixture over an ion-exchange column to separate and collect the product (col. 7, lines 21-24.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the device and method taught by Knapp in view of Yon-Hin to perform the assay taught by Beers, as would be desirable for discovering compounds to treat bone wasting diseases as taught by Beers.

### *Allowable Subject Matter*

Claim 13 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### *Conclusion*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Parsi et al., 5,203,976, Pall, 3,591,010, and Dantsker et al., 6,499,499, all disclose a process of making an ion-exchange column by flowing ion exchange materials into a region. Hu et al., 5,114,855, teaches polyacrylamide with modified charge (col. 6, line 30). Bradwell, 4,053,512, teaches that polyacrylamide is not itself ion, but can be modified to form ionic polymers.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on M-Sat 11-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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12/13/04